Integrative Modeling Approach to Assessing Cardiotoxity Risk

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Modeling and Simulation, Novartis

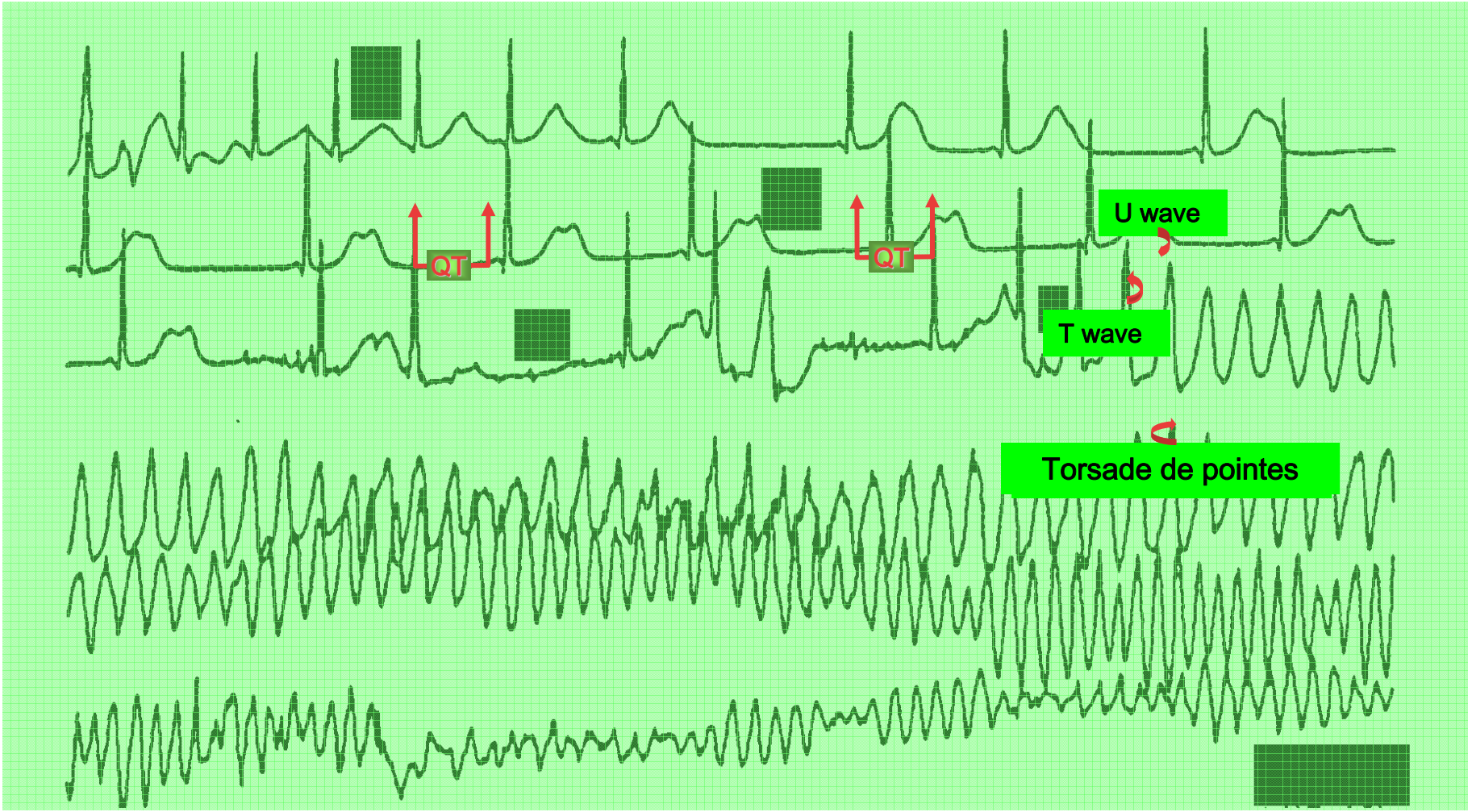
Problem of QT prolongation and arrhythmias

- Prolonged QT has been accepted as biomarker for sudden death!
- It is associated with a potentially fatal ventricular arrhythmia = *Torsades de Pointes* (TdP)
- Major regulatory concern
- Question is:
  - Who is at risk? Risk quantification?
  - When?
  - Which drugs and at what exposures?

Identify 'signal' for arrhythmia

- IKr (HERG) block →
- Prolongation of action potential duration (APD) →
- Increase in QT interval →
- TdP

QT prolongation, *Torsades de Pointes* and ventricular fibrillation.



Pre-Clinical Drug Cardiac Safety Assessment: Work flow on the Experimental Side

CHANNEL ASSAYS (IC_{50} values)

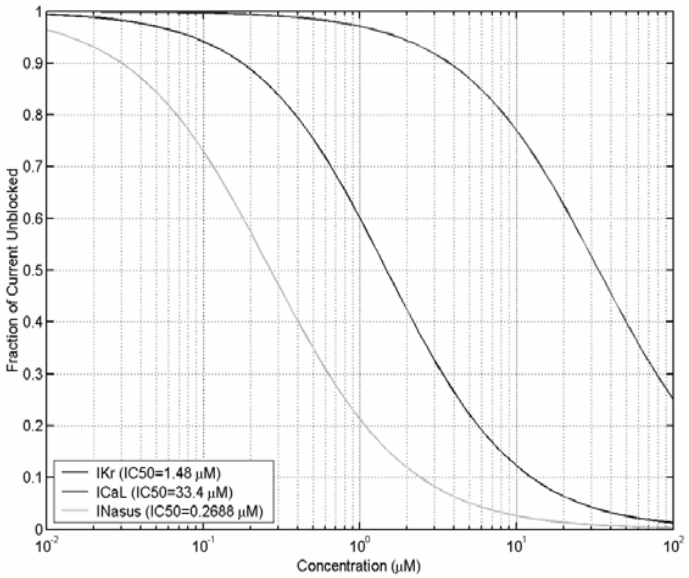
- **HERG (I_{Kr})**
- **Others (I_{Na})**

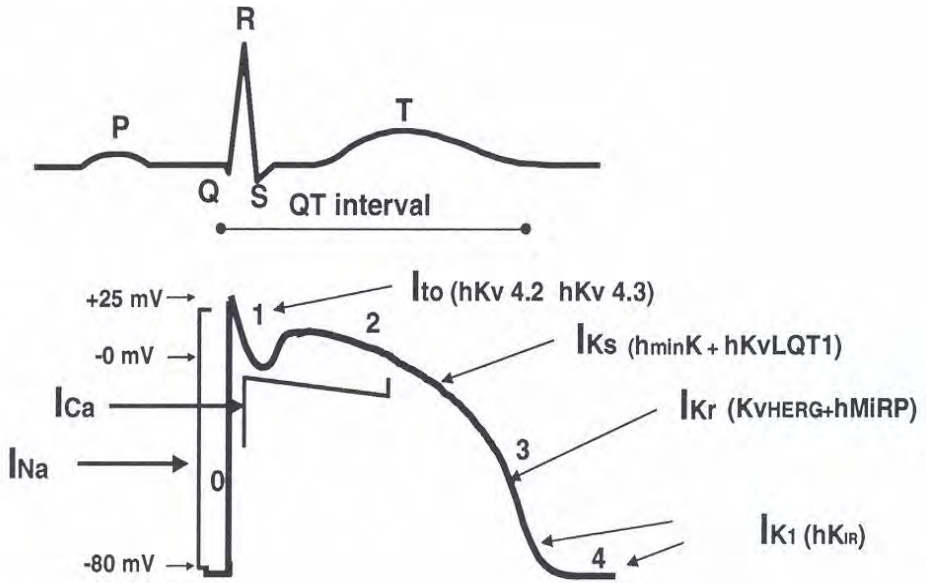
CARDIAC CELL/TISSUE ASSAYS

- **Ventricular myocytes (various species, incl. human)**
- **Purkinje fiber (various species)**
- **Papillary muscle, ventricular strips**

ORGAN LEVEL ASSAYS (Higher level data, incl. ECG)

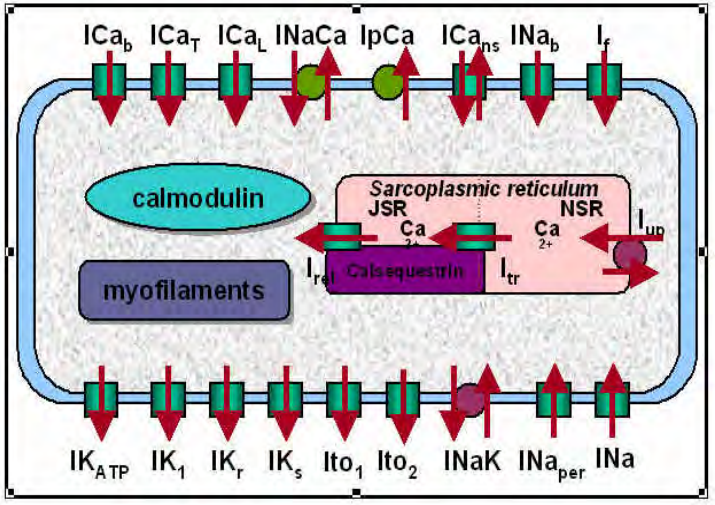
- **Langendorff type preparations**
- **In vivo dog telemetry**

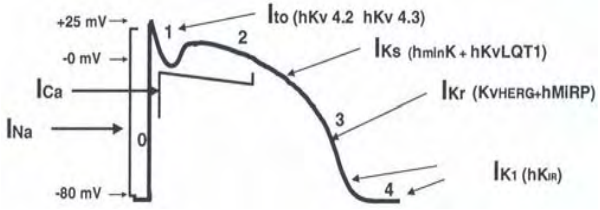


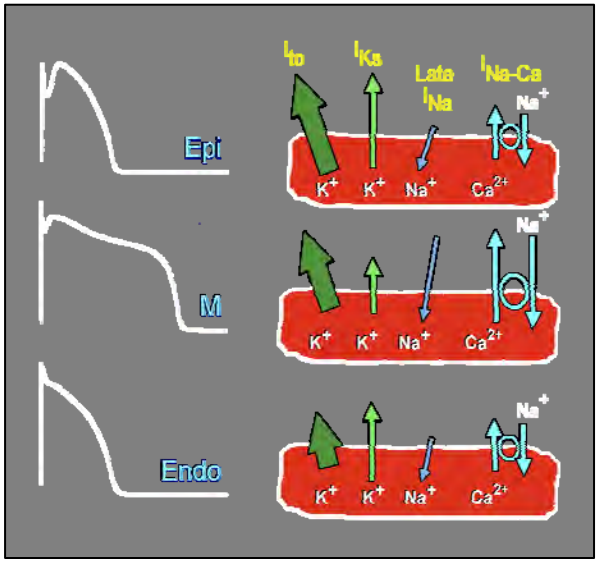


Complexities of information integration

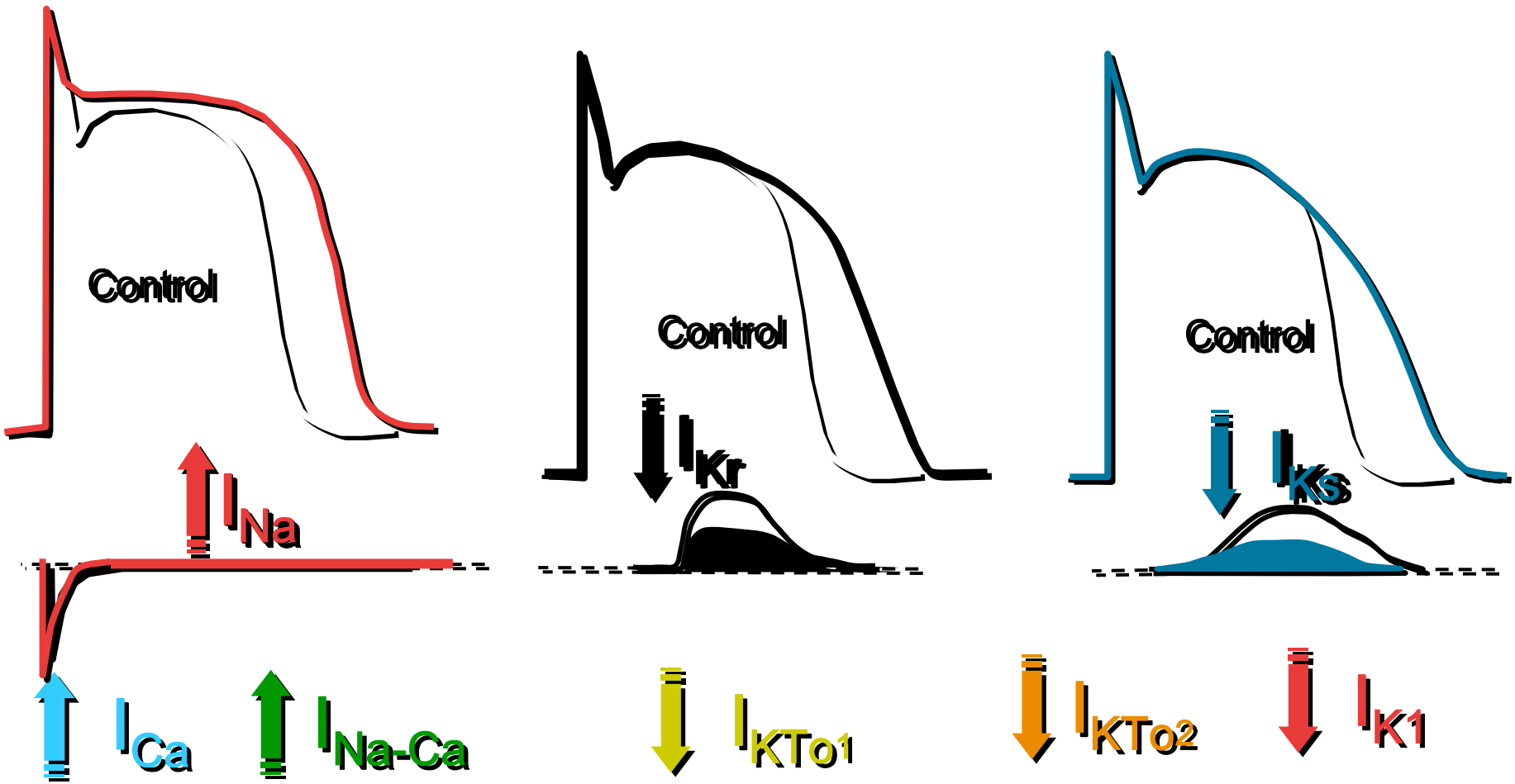
- I_{Kr}: often the only channel directly tested at early screening stage
- Drugs often affect other channels: I_{Ks}, $I_{Ca\text{-}L}$, late $I_{Na\text{-}sus}$, all important in repolarization!
- I_{Kr} "red flag signal" ➔ Mixed effects on other channels may worsen OR improve effects on APD and QT
- NO I_{Kr} "signal" ➔ Doesn't imply one is necessarily "safe" at the APD or QT level!
- Spatial heterogeneity in channels, from endo- to mid- to epi-cardiac cells across ventricular wall
- Many other physiological variables ➔ heart rate, disease/genetic status, gender, nutrition, diurnal







Ion Currents Impacting Prolongation of Myocyte Repolarization

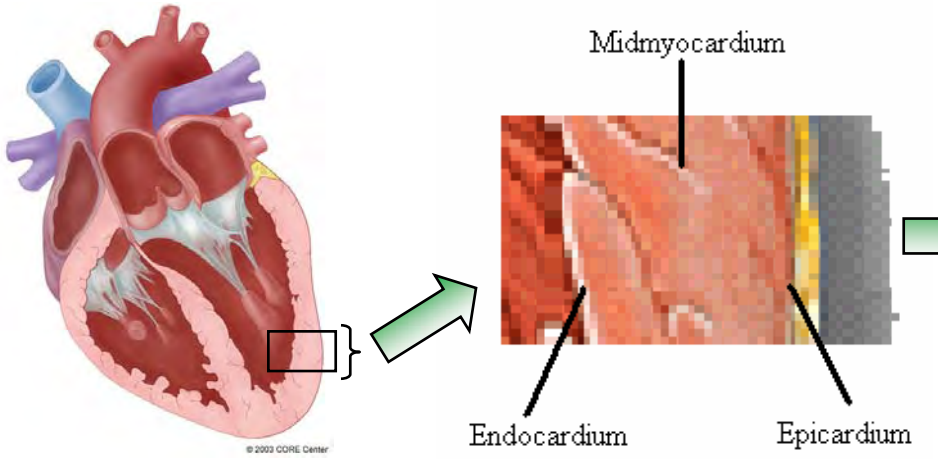


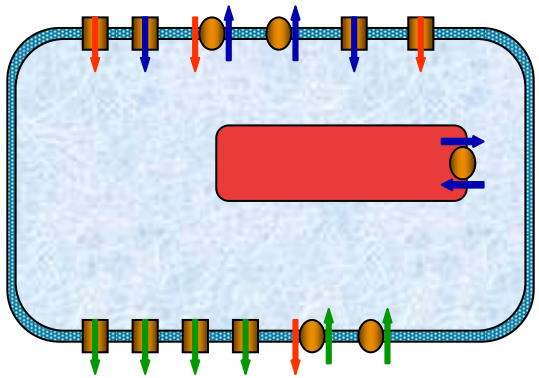
How do we tackle the problem of integrating information that may be pointing to different conclusions?

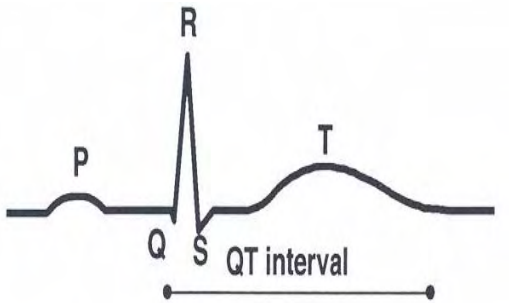
What is a modeling platform?

- Model of a biological system of interest
- Is created in a flexible manner that allows taking of new data and information
- Incorporate uncertainty of scaling:
  - across species
  - IVIV
  - inter-subject variability
- Potential to be re-usable for multiple projects
- Necessarily span multiple space and time scales
  - to include drug targets
  - to include clinically relevant points, such as biomarkers

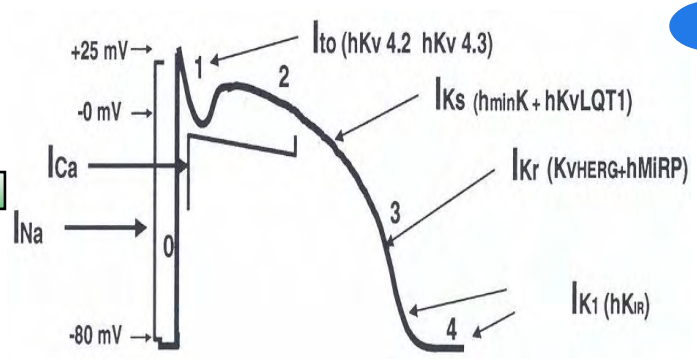
Conceptual framework of modeling platform







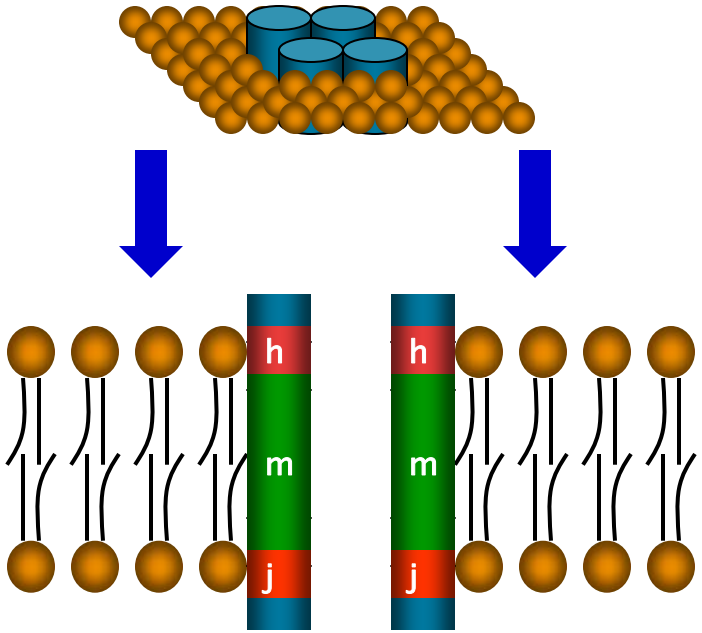
$$\iiint f(x, y, z, t)\, dx\, dy\, dz$$



Forward vs. Reverse Mode

Models of membrane gating

- **Non-Linear Channel Model - Na**



$$\alpha_m = \frac{1}{1 + e^{(-60-V)/5}}$$

$$m_{open} \underset{\beta_m(V)}{\overset{\alpha_m(V)}{\rightleftharpoons}} m_{closed}$$

$$h_{open} \underset{\beta_h(V)}{\overset{\alpha_h(V)}{\rightleftharpoons}} h_{closed}$$

$$j_{open} \underset{\beta_j(V)}{\overset{\alpha_j(V)}{\rightleftharpoons}} j_{closed}$$

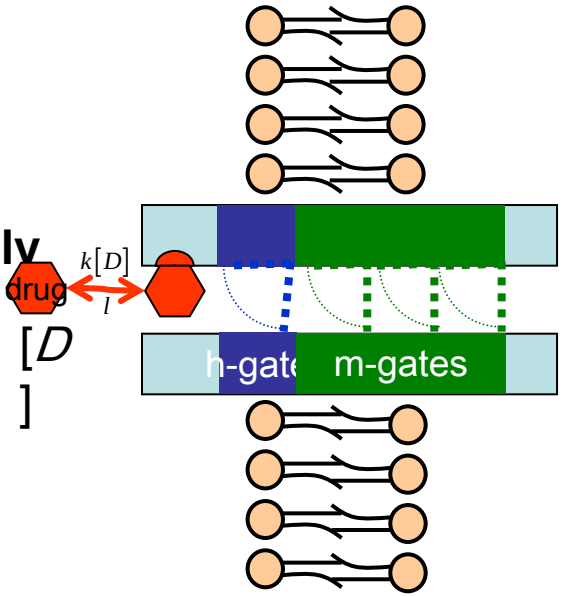
$$I = G\, m^3\, h\, j\, (V - V_{eq})$$

Conductance — Open Fraction — Driving Force

Work of many academic researchers- from 1962 till now!

Modeling of drug effects

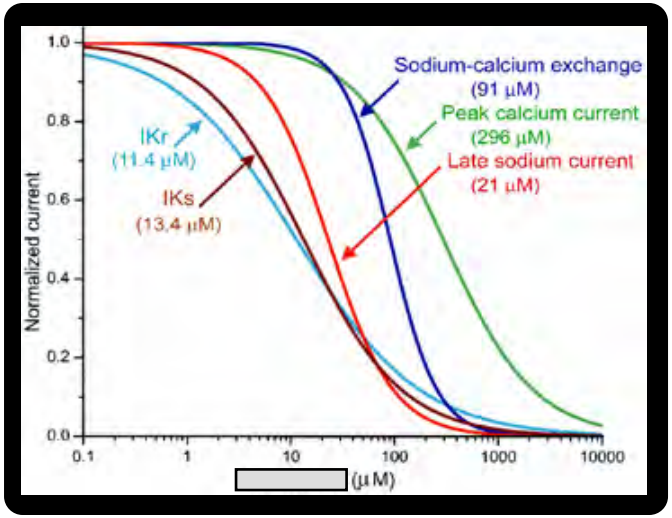
- I_{max} approach taken:
  - (1-b) modifier added to specific current
    - Can actually be applied to a single gate only
  - b defined as a percent of channels blocked
    - b_∞ is the steady state value



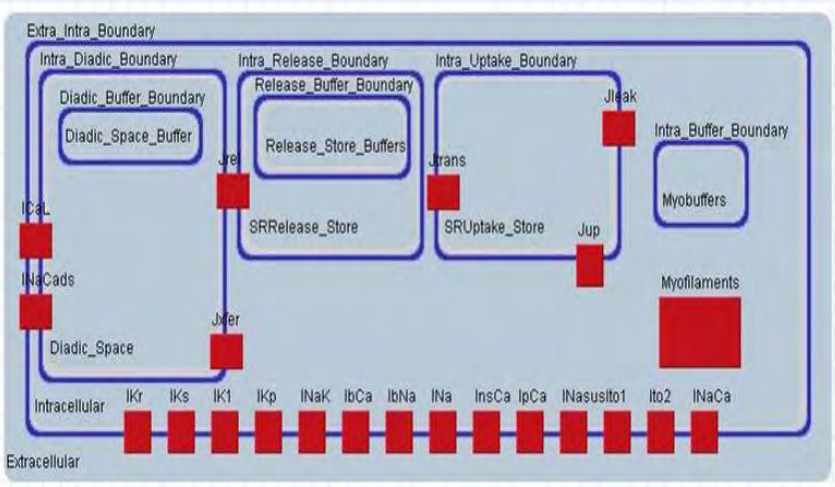
$$I = G\, m^3\, h\, j\, (V - V_{eq}) \times (1 - b)$$

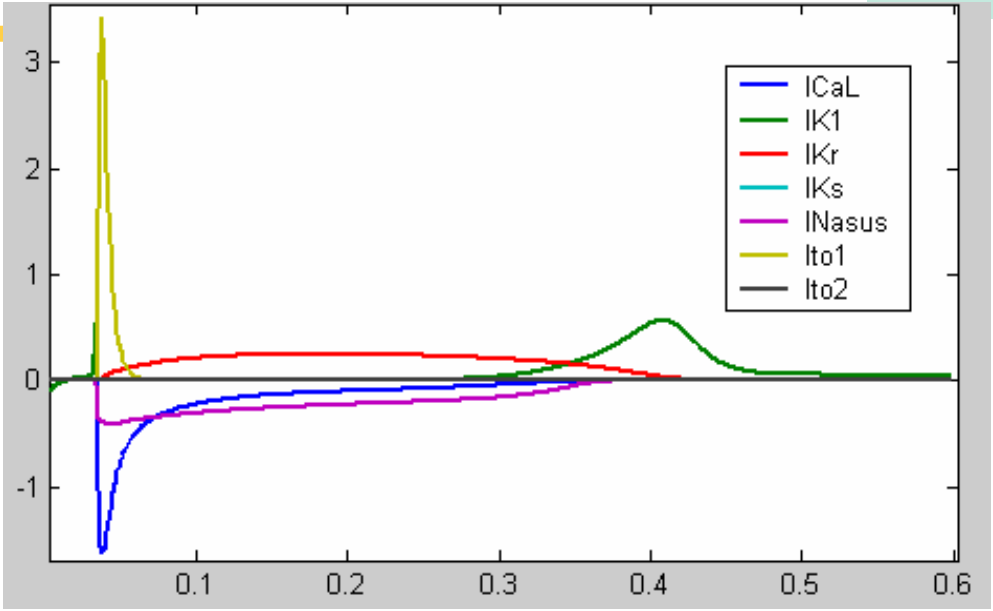
Conductance — Open Fraction — Driving Force — Drug Effects

$$b_\infty = 1/(1 + IC_{50}/[D])$$



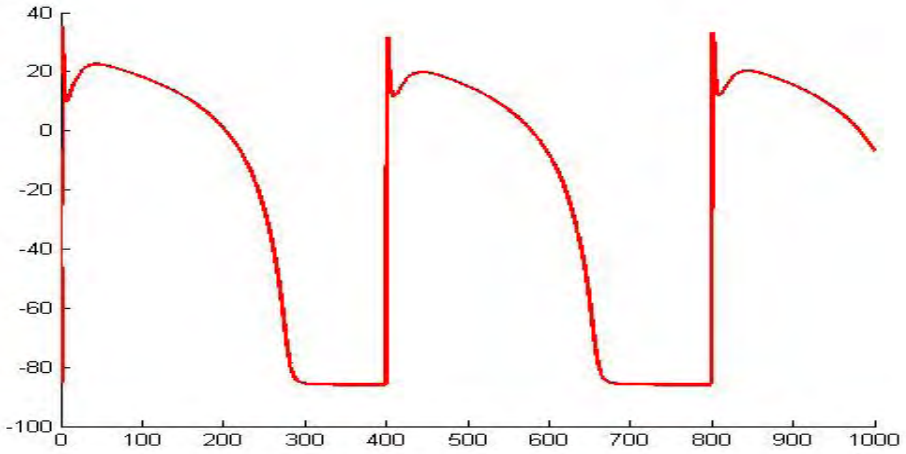
Integrating channels into a cell model





Cell membrane as a capacitor

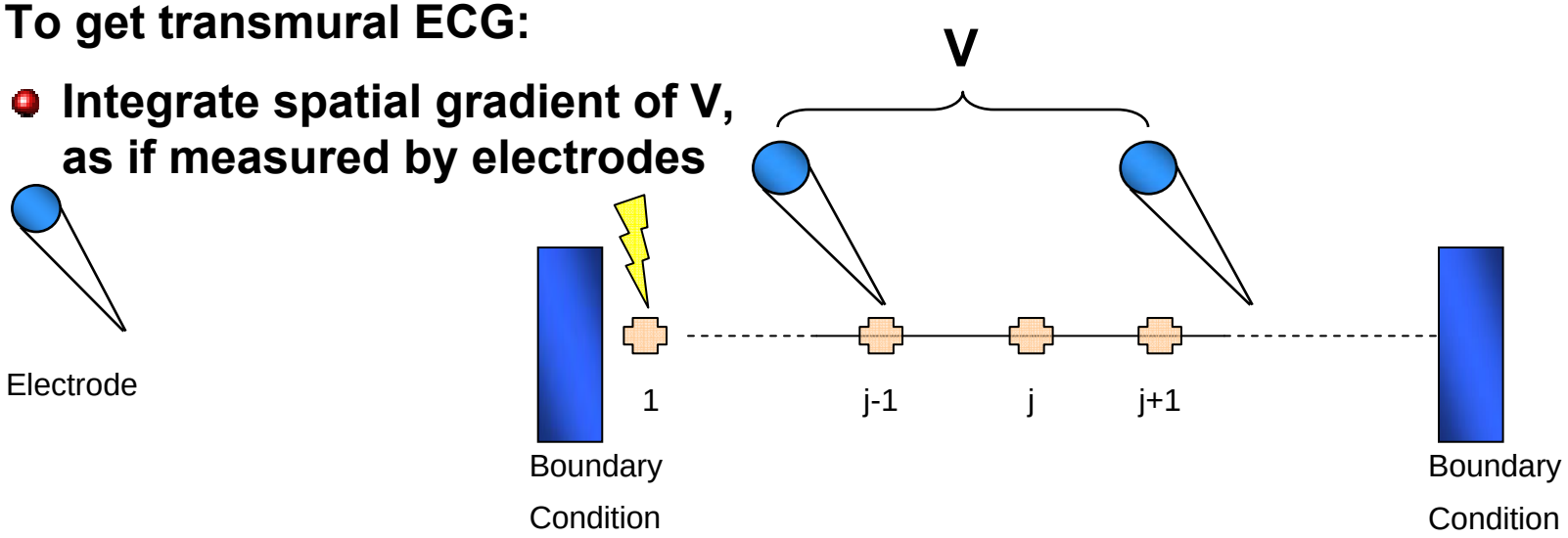
$$\frac{dV}{dt} = -\frac{1}{C_m}\sum I_{curr}$$



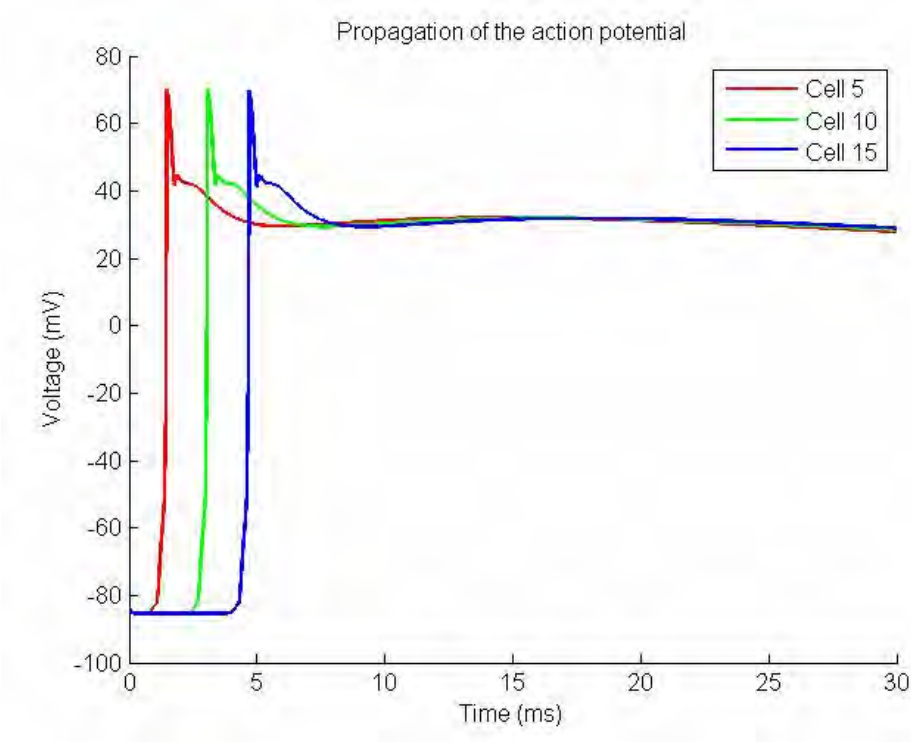
action potential V(t)

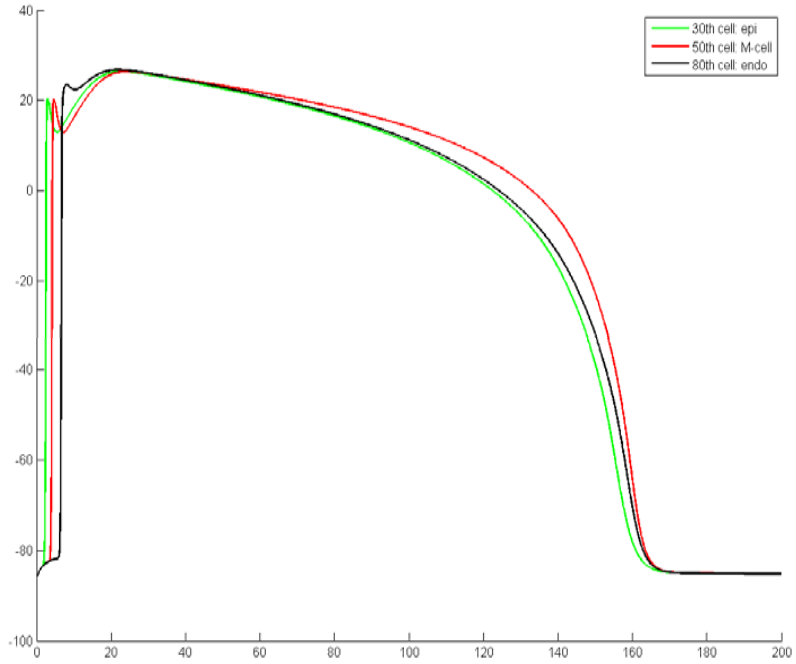
Spatial modeling: one dimensional approach

- Create a model with a few cells in series
- Stimulus applied to first cell
- Measure voltage in each cell as membrane capacitance changes
  - Spatial gradient of voltage develops over time
- To get transmural ECG:
  - Integrate spatial gradient of V, as if measured by electrodes



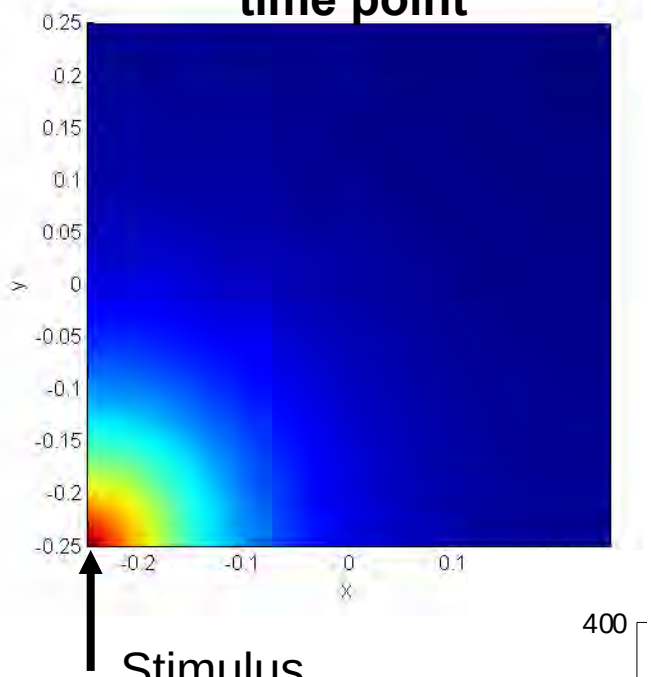
Spatial Modeling: Results for multicellular tissue



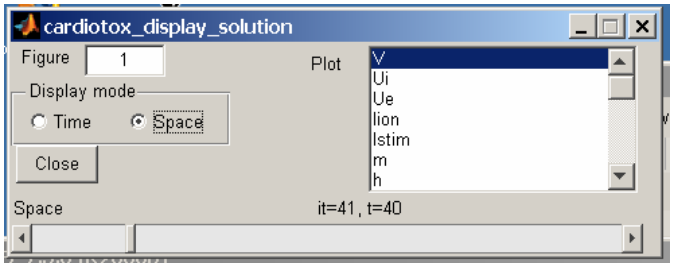


2D simulation with an accurate cellular model

Spatial profile at a specific time point

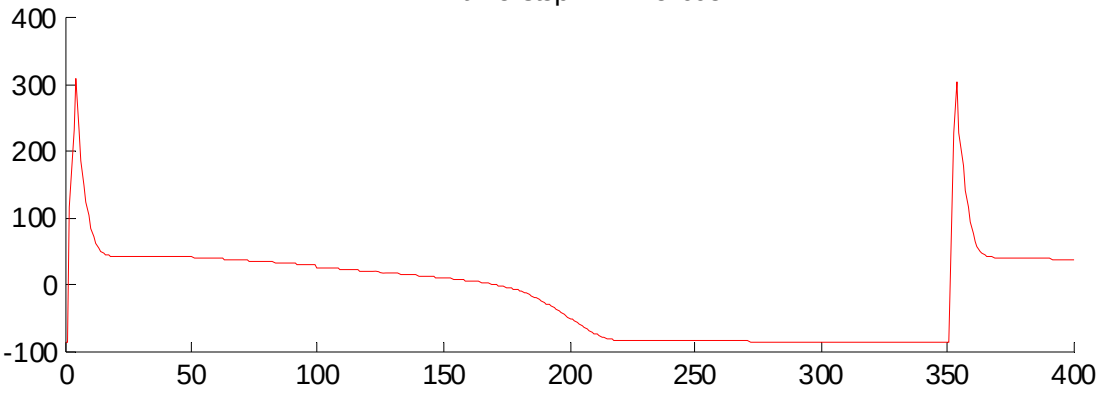


Stimulus



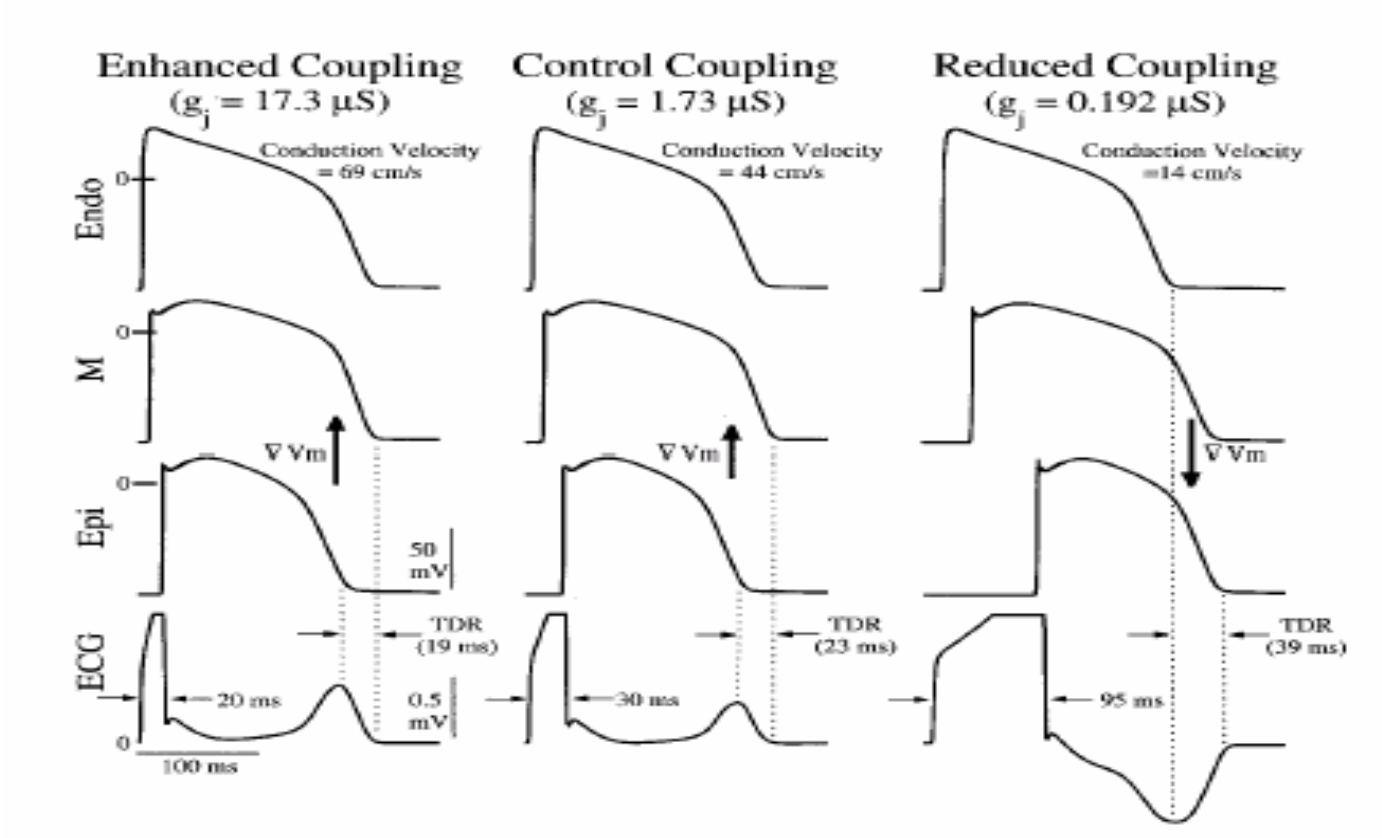
The model allow you to visualize the space and time propagation of the AP for the electrical potential but also for the all others variable of your model

Min time step=7.441e-005



Time profile at stimulus location

Effect of coupling



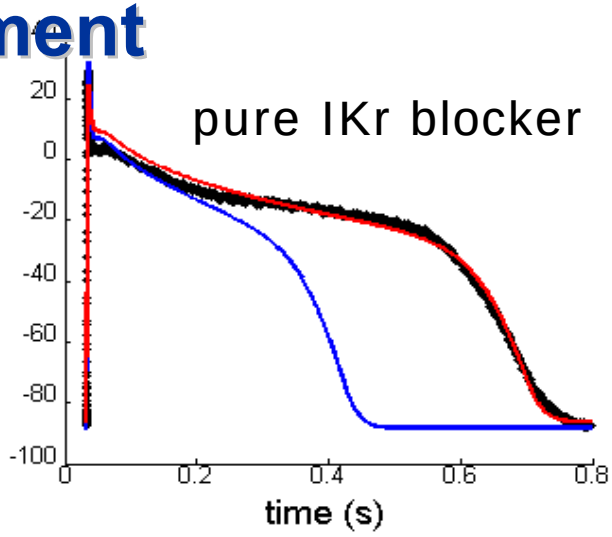
From Gima & Rudy, “Ionic Current Basis of Electrocardiographic Waveforms: A Model Study,” Circ Res 2002; 90:889-896.

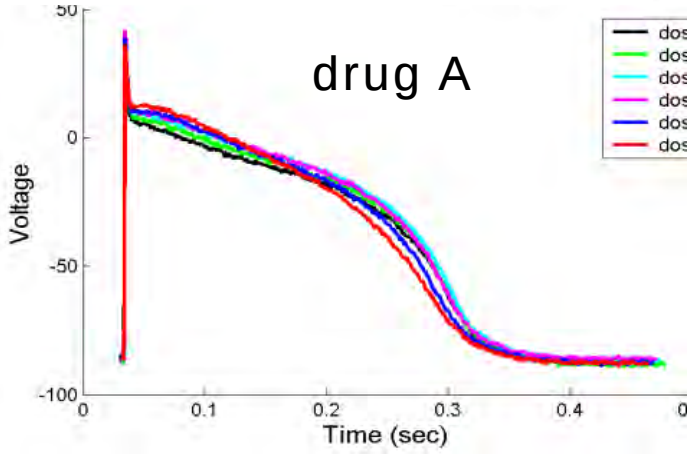
Study case for cardiotox assessment

Data for 2 drug candidates

- **+ HERG/IKr block**
  - **1.48 mM (Drug A) and 1.82 mM (Drug B)**
- **no Purkinje Fiber APD prolongation!**
  - **paced at 0.5, 1.0 Hz,**
  - **drug concentration: 0, .1, .3, 1.0, 3.0, 10 mM**
- **Evaluation of risk**
- **Compound prioritization**

- **Constraints in model:**
  - **No full experimental IC50 profile**
  - **Building a new model of Purkinje fiber**
  - **Characterization of variability**
- **Goal: provide *in silico* risk assessment with available data and models**





→ **Novel**: applications of parameter estimation to *in silico* cardiac safety assessment
Bottino et al, PBMB (2006) 90(1-3):414-43

Novel workflow in platform development

myocyte model

estimate 14 conductances (G)

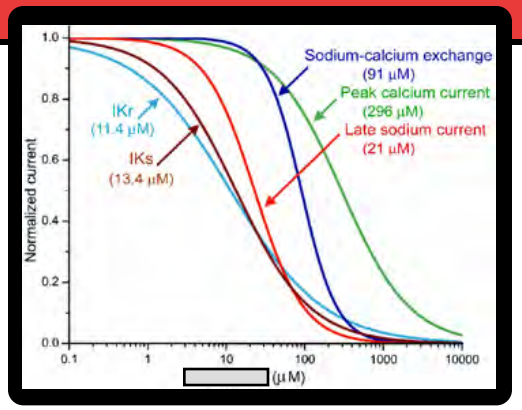
Purkinje model

estimate 14 conductances (G)

CPF Prep model

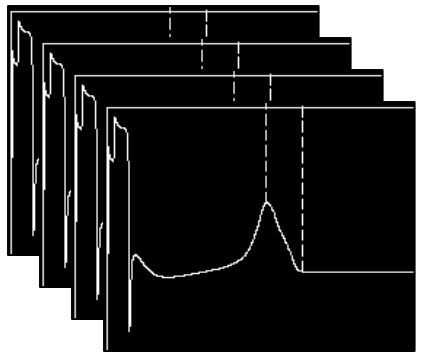
estimate 5 IC50s

Predicted drug block



FORWARD MODEL

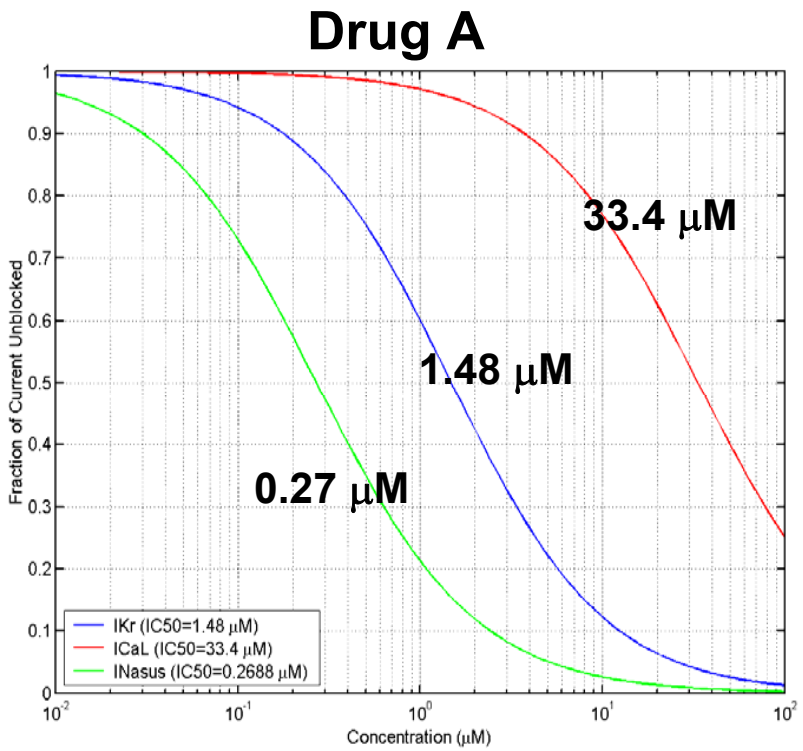
multiple risk factor combinations

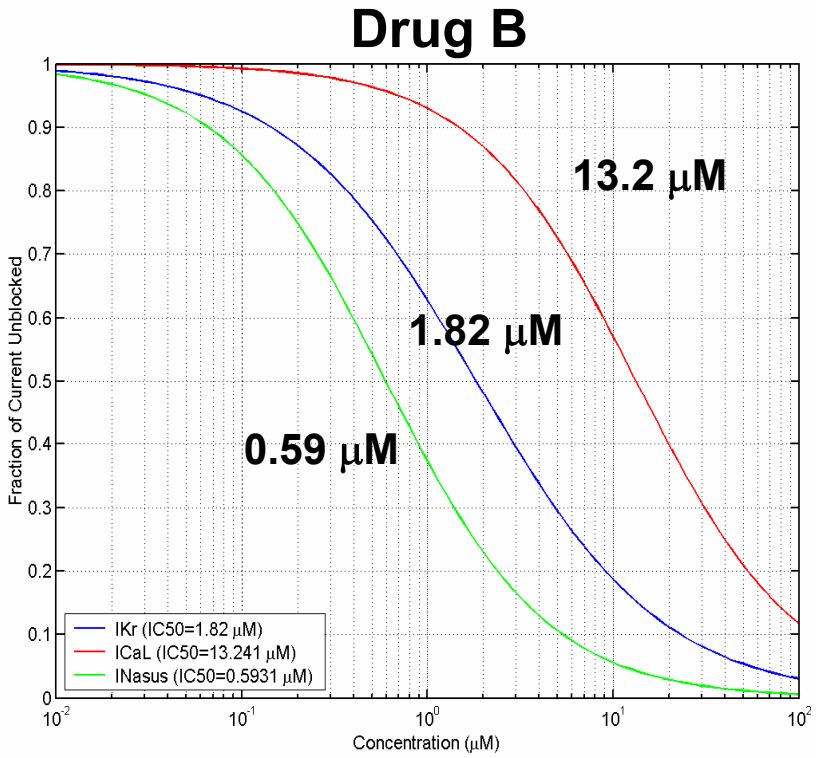


arrhythmia predictions

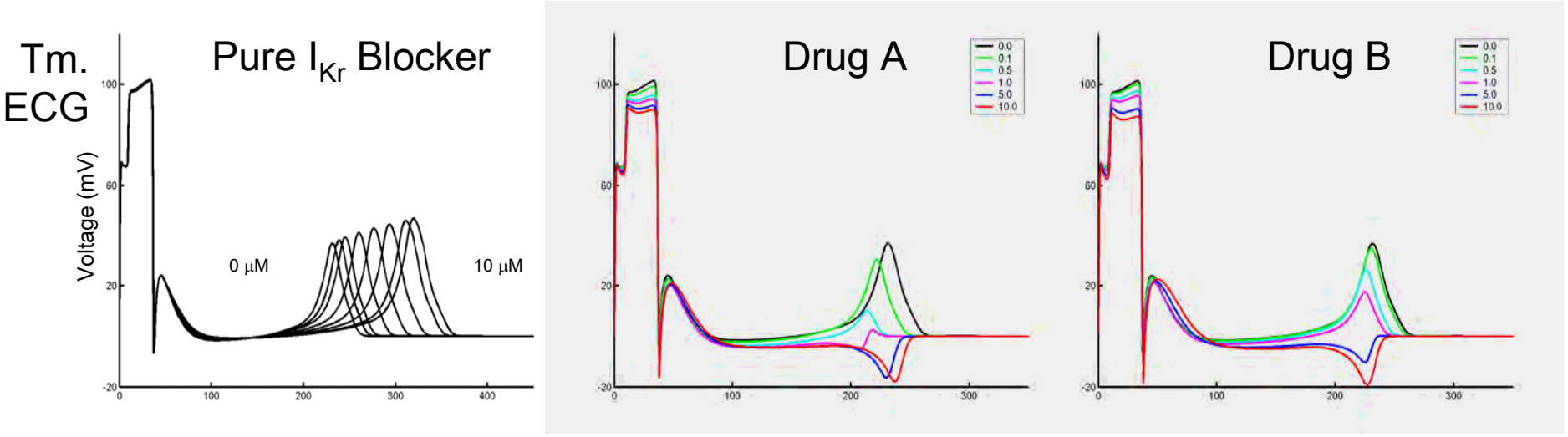
Reverse-engineering results

➔ Significant inhibition of I_{Kr}, $I_{Ca\text{-}L}$, $I_{Na\text{-}sus}$ by both drugs
➔ Dose-response estimates for key currents: important for AP repolarization





Forward-engineering



- **Pure I_{Kr} blockers prolong the QT interval (left panel)**
- **Both drugs act to shorten the QT interval and reduce the amplitude of the T wave (at high doses there is also inversion)**
- **At higher concentrations of Drug A (5-10 μM), shortening of the QT interval reverses but remains less than control**

Drug A vs. Drug B

- Both compounds block multiple ion currents
  - Data and model indicate significant block of I_{Kr}, $I_{Ca\text{-}L}$ and $I_{Na\text{-}sus}$
  - Stark contrast to "null-hypothesis" of pure I_{Kr} block
- No dose-dependent QT prolongation or increase in TDR
- Confidence intervals for Drug A smaller *vs.* Drug B
  - Confidence in predictions is better for Drug A
- Experimental Confirmation ☺

Fast I_{Na}	Drug A: IC_{50} = 2.30 μM	Late I_{Na}	Drug A: IC_{50} = 0.23-0.46 μM
	Drug B: IC_{50} = 4.48 μM		Drug B: IC_{50} = 0.45-0.90 μM
		Model	Drug A: IC_{50} = 0.27 μM
			Drug B: IC_{50} = 0.59 μM

Conclusions

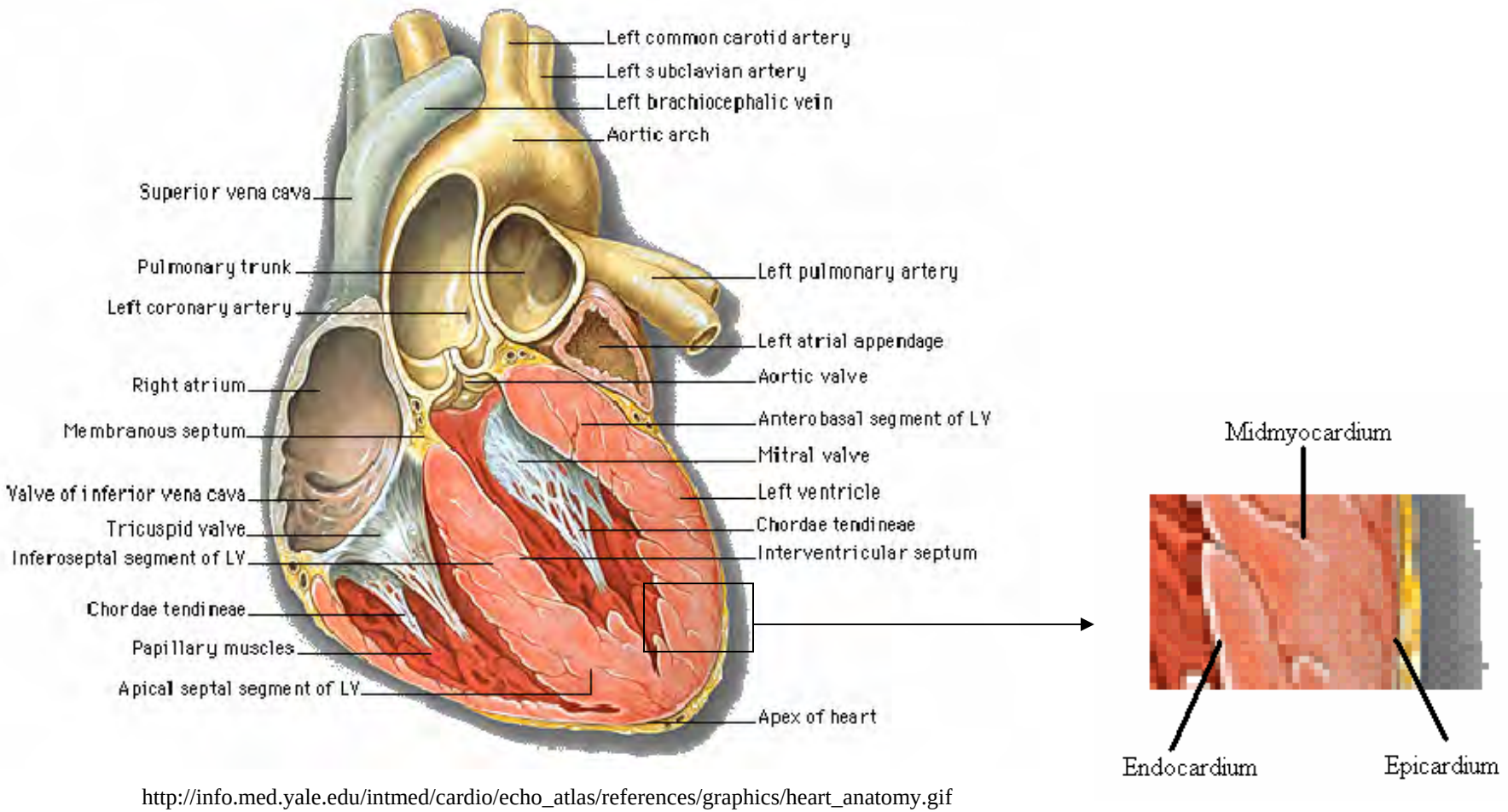
- Modeling can resolve contradiction between experimental readouts
- Results in excellent agreement with independent experiments (validation)
- Can expand model to introduce uncertainty and compare with clinical results
- Modeling provides new insight into system
- Modeling provides flexible framework
- Adapt models to reflect currently used experimental assays
- Impossible to implement such efforts without tremendous amount of insights coming from previous research efforts

Contributors

- Berengere Dumotier
- Ruben Bibas
- Michael Deutsch
- Dean Bottino
- Denis Noble
- Natalia Trayanova
- Scott Lett
- Andy Stamps
- Christian Penland
- Gabriel Helmlinger

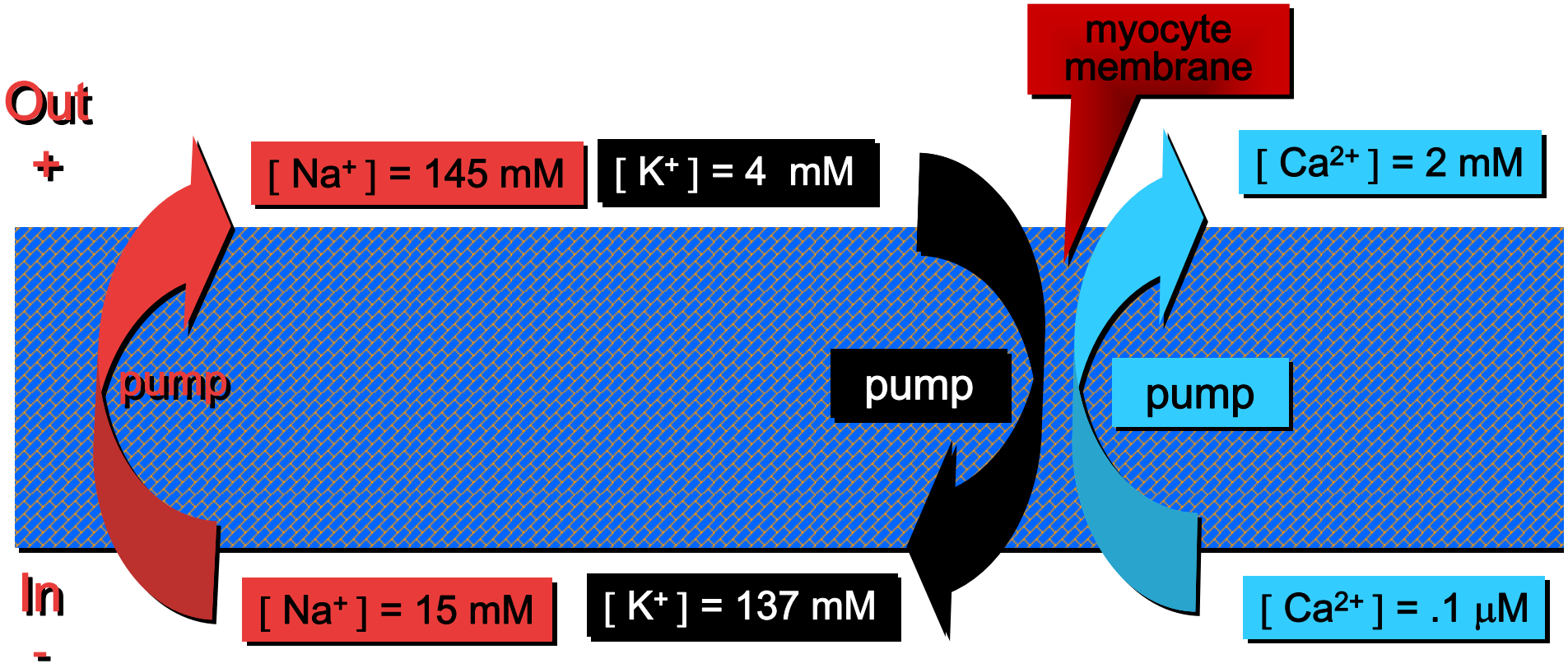
Backup Slides

Heart physiology & membrane dynamics



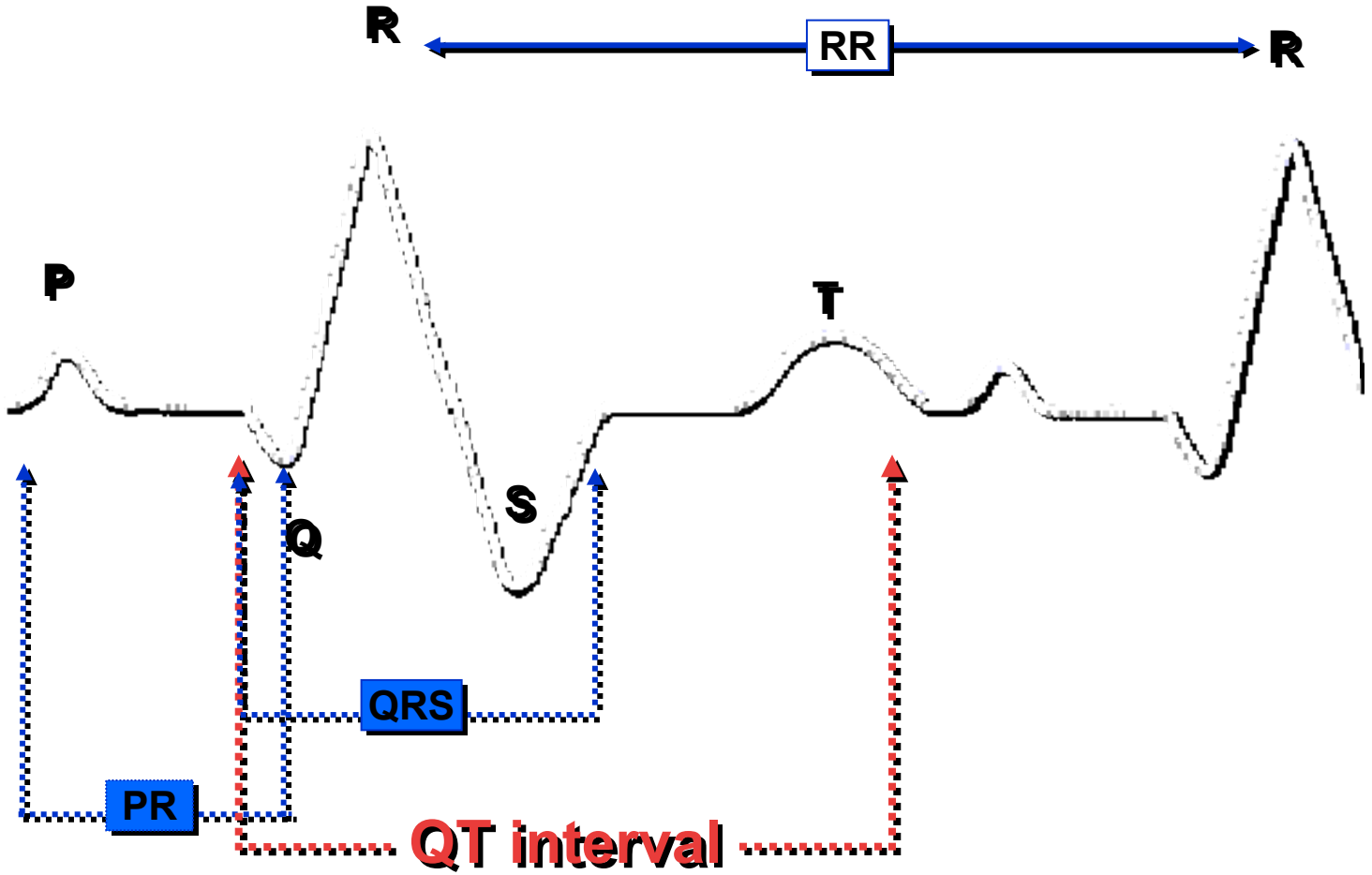
http://info.med.yale.edu/intmed/cardio/echo_atlas/references/graphics/heart_anatomy.gif

Trans-membrane gradients of electrolyte concentrations



Membrane potential (resting potential/action potential) determined by trans-membrane ion gradients

Waves and time intervals constituting the electrocardiogram

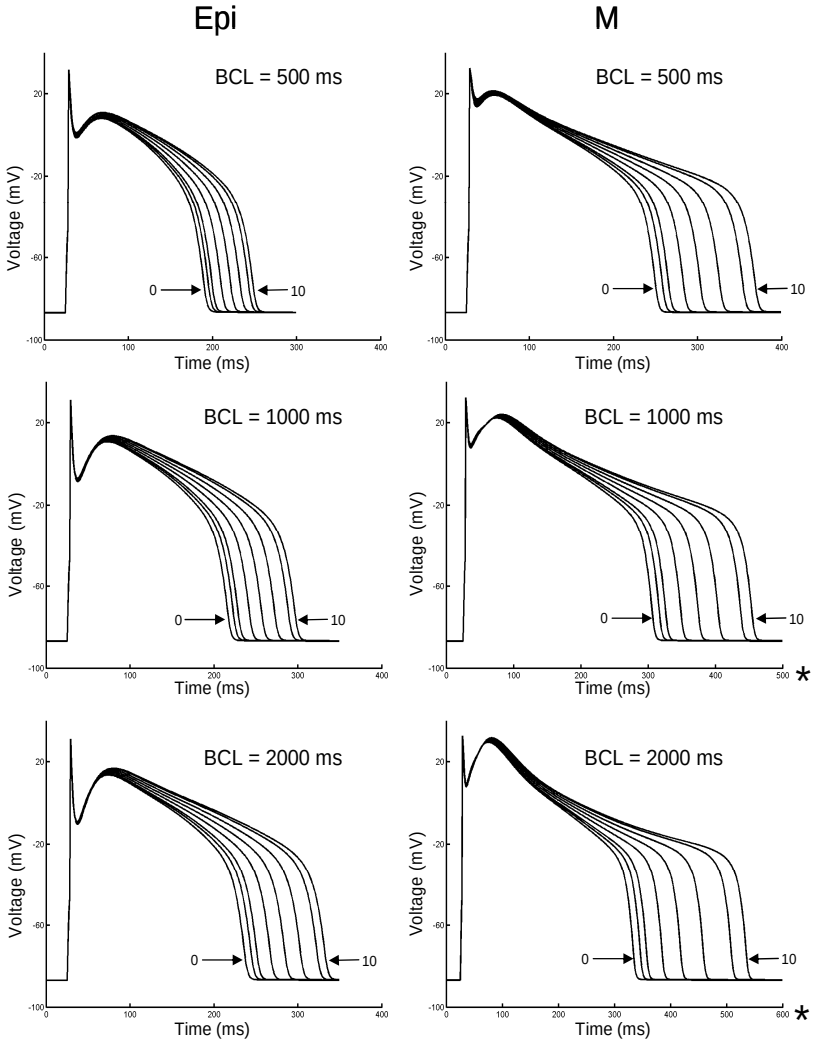


Development of canine purkinje fiber model: assumptions

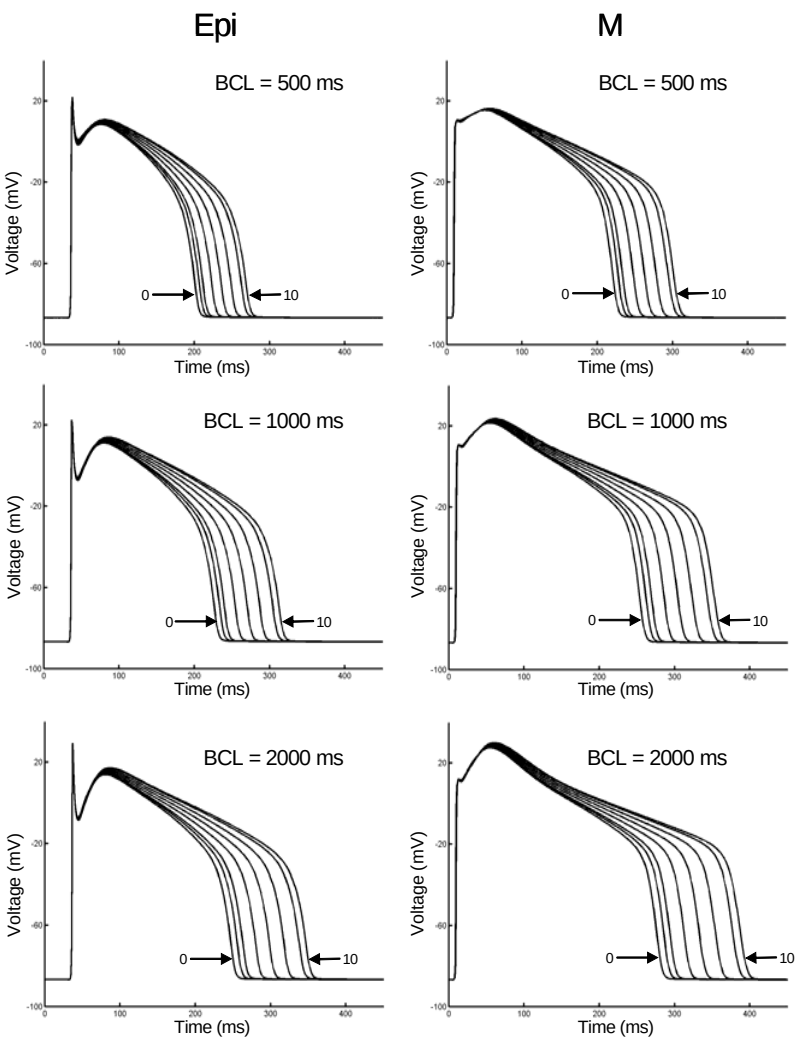
- **Mechanisms within the existing endocardial myocyte model are similar to those of canine Purkinje fiber**
  - **Differences can be approximated by changing 14 conductance parameters**
- **Drugs act via a sigmoidal dose-response relationship to inhibit 6 currents (I_{Kr}, I_{Ks}, I_{to}, $I_{Ca\text{-}L}$, $I_{Na\text{-}Ca}$, $I_{Na\text{-}sus}$)**
  - **These currents suffice to predict the action of a drug on ventricular myocytes and Purkinje fibers**
- **Dose-response parameters from HERG assay and Purkinje fiber parameter estimates can be used in ventricular myocyte models**
- **The chosen error functions are a good measure of the quality of fit of the model to action potential data**

Pure I_{Kr} blocker" hypothesis (Drugs A & B) ➔ not good

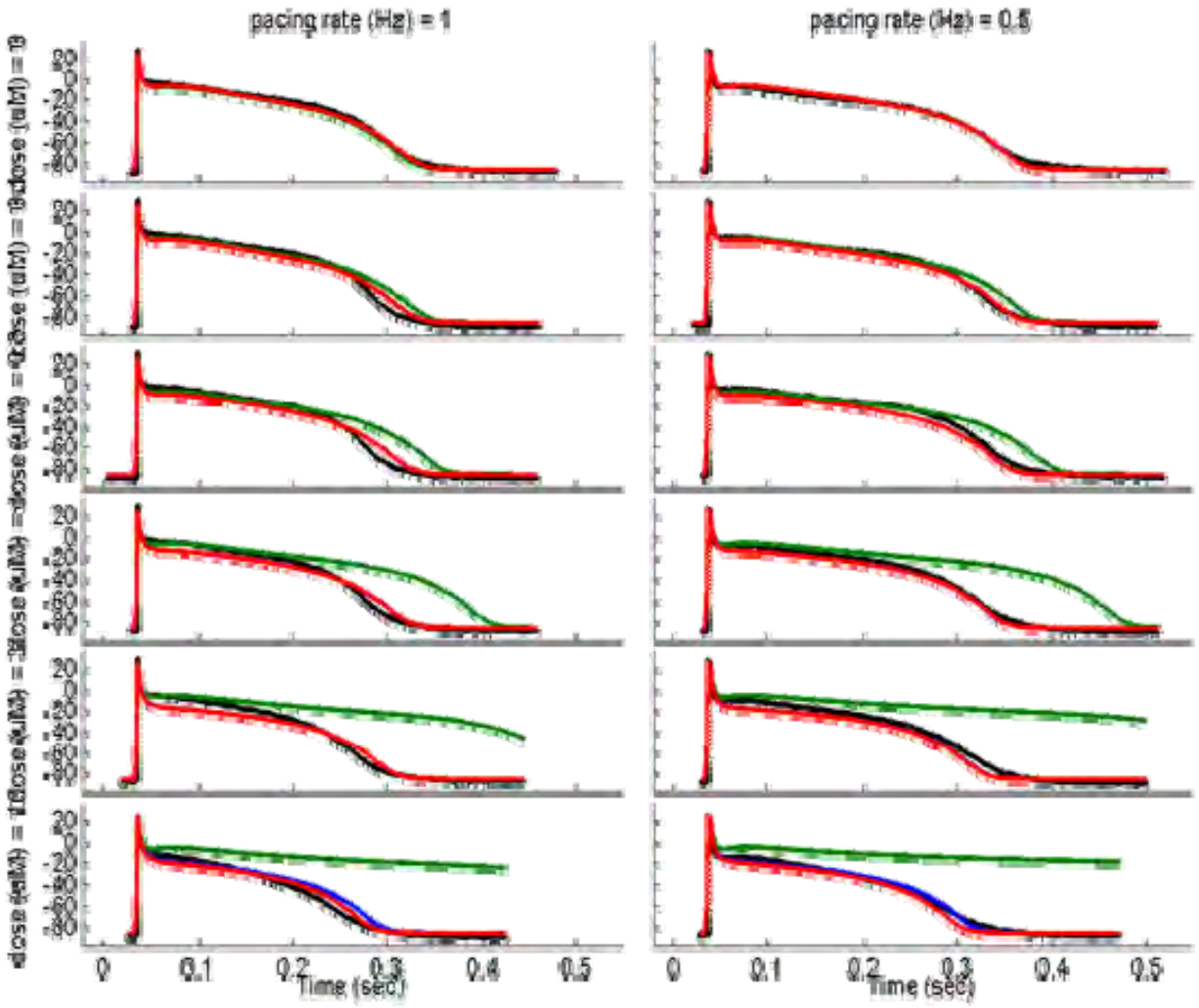
Isolated Cell Models



Cells Coupled Through the Cable Mode



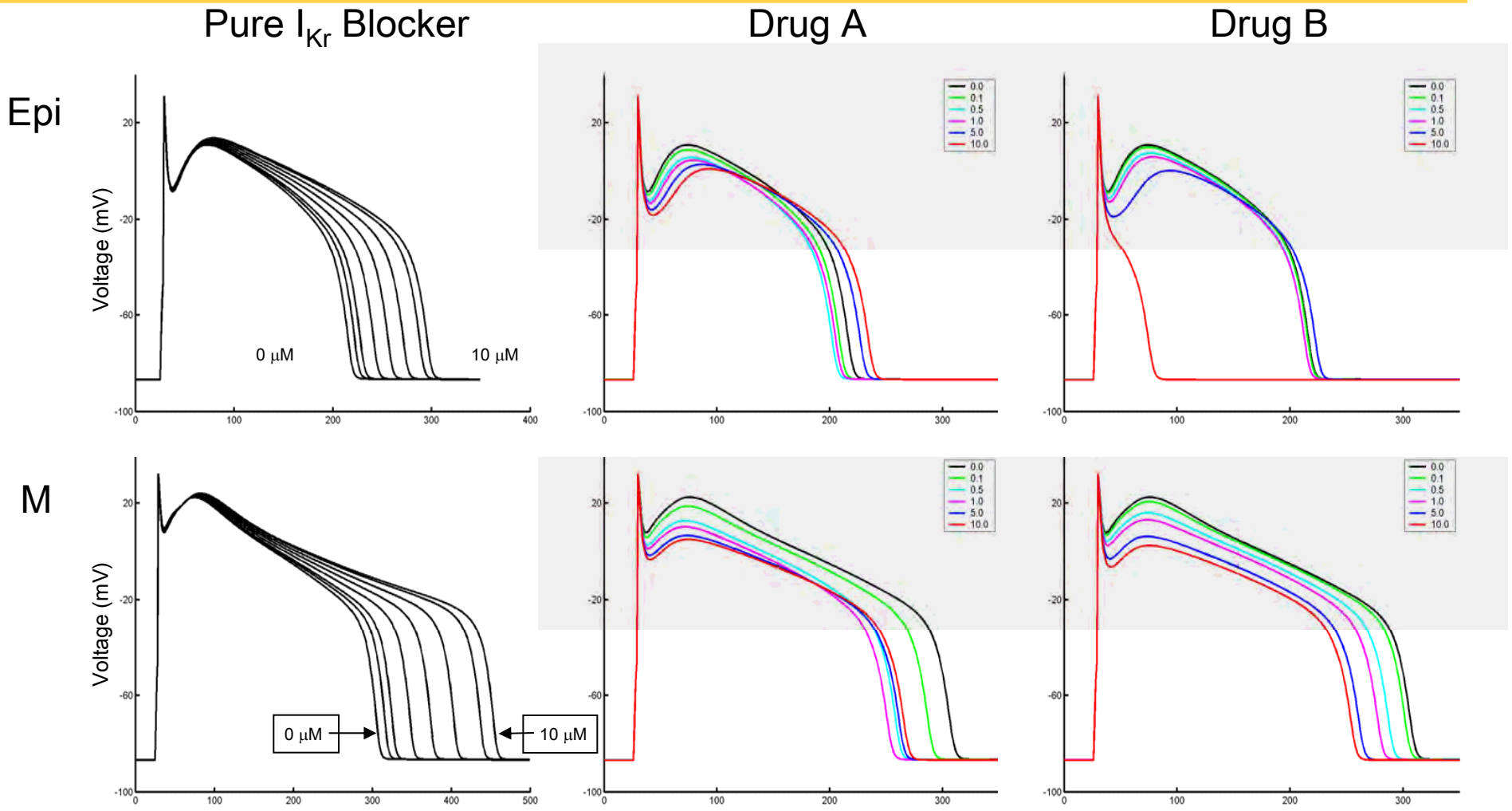
Drug A IC50 profile fits



Best score=.01

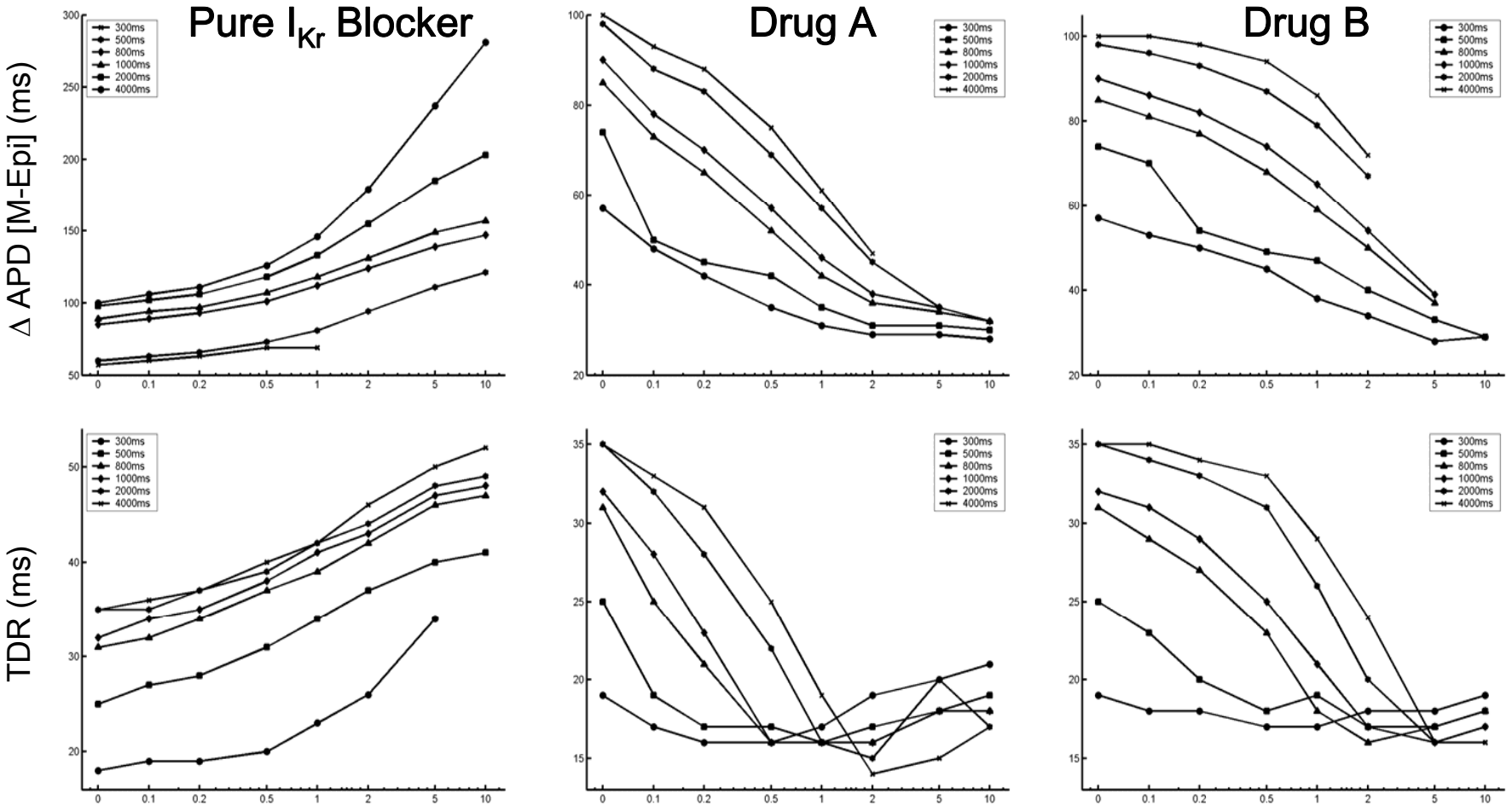
Herg block alone=0.6

Forward-engineering (I)



In contrast to pure I_{Kr} blockers, which prolong the action potential (severely so in M cells), Drug A & Drug B either do not affect or even shorten action potentials in isolated cells

Forward-engineering (III)



- **The difference in APD between isolated epicardial and M cells is, in this example, consistent with the TDR in the 1-D cable**